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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GRUN, JAMES LESLIE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,144	HICKOK ET AL.	
	Examiner	Art Unit	
	James L. Grun	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/5/04;02/24/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The Information Disclosure Statement filed 05 October 2004 was considered to the extent it was possible to weed through the extensive listing of patents and publications irrelevant to the invention as instantly claimed. Applicant is invited to identify and point out documents of particular relevance to the instantly claimed invention not cited by the Examiner herein.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Claims 1-5, 6-12, 15-24, 26-44, 47, and 49-64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, particularly the invention commensurate in scope with these claims.

The prior art would suggest that an ability to prolong a pregnancy at risk for preterm delivery is not a property known or common to the laundry list of progestational agents disclosed by applicant (see e.g. Goldstein et al. or Keirse in this regard). "[T]here are large differences among the many agents considered to be progestational on the basis of pharmacological tests" (Keirse, page 149), including differences in teratogenic, metabolic, or hemodynamic effects of

natural progesterone compared to artificial progestagens (da Fonseca et al., page 419). Absent further guidance from applicant, and random experimentation unguided by applicant, experimentation which is undue, one would not be assured of the ability to practice the invention commensurate in scope with these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 10, 11, 15, and 17-64 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1-7, the metes and bounds of the invention intended as encompassed by applicant are not clear because no components, only an intended use, are recited for the kit. In claim 2, only an antibody is recited in the kit and it remains unclear what other components are comprised in the "kit" and their interrelationships. In these claims "the presence" lacks antecedent basis.

Claim 4 provides no further limitation of the combination as it only limits the intended use and does not appear to affect the components. In this claim, "the" elements lack antecedent basis.

In claims 10, 11, and 15 it is not clear if the additional antibodies are specific for the same antigen or a different antigen.

In claim 11, the additional antibody alternatives do not further limit the anti-(fetal restricted antigen) antibody of claim 10.

In claims 17-25 and 30-34, "the" level or corpus luteum, placenta, or adrenal cortex lack antecedent basis.

In claim 21, "the" ratio lacks antecedent basis.

In claims 26-29, "the" level lacks antecedent basis.

In claims 35-64, "the" level lacks antecedent basis.

In claim 36, "the" elements lack antecedent basis.

In claim 39, "the" start lacks antecedent basis.

In claim 43, "the" onset lacks antecedent basis.

In claim 49, "the" therapeutically effective amount lacks antecedent basis.

In claims 53 or 54, "the" elements lack antecedent basis.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 16 is rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Meis et al. (Am. J. Obstet. Gynecol. 187: S54, 2002).

Meis et al. performed the method essentially as claimed.

Claim 16 is rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Johnson et al. (NEJM 293: 675, 1975).

Johnson et al. performed the method essentially as claimed.

Claim 16 is rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Yemini et al. (Am. J. Obstet. Gynecol. 151: 574, 1985).

Yemini et al. performed the method essentially as claimed.

Claim 16 is rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Noblot et al. (Eur. J. Obstet. Gynecol. Rep. Biol. 40: 203, 1991).

Noblot et al. performed the method essentially as claimed.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-13, 15-19, 22-26, 30-31, 33-44, and 47-64 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Leavitt et al. (WO 94/17405) in view of any of Johnson et al. (NEJM 293: 675, 1975), Meis et al. (Am. J. Obstet. Gynecol. 187: S54, 2002), or Keirse (Br. J. Obstet. Gynaecol. 97: 149, 1990), and further in view of Weiner et al. or Andersen et al.

The invention as instantly disclosed, with regard to determinations of fetal fibronectin or total fibronectin as biochemical markers of impending imminent preterm delivery and of insulin-like growth factor binding protein-1 to determine fetal membrane status to aid clinical decisions regarding administration of treatments to prolong pregnancy in pregnant patients at 12 to 37 weeks gestation (see e.g. pages 4-6, 8), is essentially as disclosed and claimed in the reference of Leavitt et al. except for the instant alternative use of estriol determination as a biochemical marker of impending preterm labor. In contrast to the invention as instantly disclosed and claimed, Leavitt et al. does not teach the specific use of progestational agents as the agents to prolong the pregnancy determined to be at risk for preterm delivery in the absence of ruptured membranes.

Any of Johnson et al. (NEJM 293: 675, 1975), Meis et al. (Am. J. Obstet. Gynecol. 187: S54, 2002), or Keirse (Br. J. Obstet. Gynaecol. 97: 149, 1990) teach the efficacy of progesterone treatments in reducing preterm delivery.

Weiner et al. or Andersen et al. teach that treatment with tocolytic agents is not beneficial (Weiner et al.) and not recommended (Andersen et al., page 346; Weiner et al.) in patients with rupture of membranes.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have tested a pregnant patient determined to have biochemical markers

indicative of impending preterm delivery for the status of the fetal membranes and to treat those patients with intact fetal membranes indicated as at risk of having impending delivery with a pregnancy-prolonging agent because of the direct suggestion in Leavitt et al. to do so. One of ordinary skill would have had ample motivation to determine and/or confirm fetal membrane rupture in patients with impending delivery, as determined by any method, because determination of ruptured fetal membranes is of unquestioned importance relating to the health of both the mother and the fetus and for the clinical management of pregnant patients, particularly in those patients at risk for preterm birth wherein a decision regarding the use of tocolytic/pregnancy-prolonging agents must be weighed (Leavitt et al., Weiner et al., or Andersen et al.). One would have been motivated to treat a patient so identified with a known efficacious pregnancy-prolonging agent, such as progesterone as taught by any of Johnson et al., Meis et al., or Keirse, in view of the direct suggestion to do so in Leavitt et al. and because one would have had an extremely reasonable expectation that a known efficacious pregnancy-prolonging agent would successfully perform its desired function in the method. It would have been obvious to formulate the reagents required to perform the method of Leavitt et al., as modified, into a kit since that is conventional for convenience, reproducibility, and economy.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 1-13, 15-22, 24-43, and 47-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leavitt et al., in view of any of Johnson et al., Meis et al., or Keirse, and

further in view of Weiner et al. or Andersen et al., as applied to claims 1-13, 15-19, 22-26, 30-31, 33-44, and 47-64 above, and further in view of Dullien (US 5,480,776).

The teachings of Leavitt et al., as modified by the teachings of Johnson et al., Meis et al., Keirse, Weiner et al., and Andersen et al., are as set forth above.

Dullien teaches determinations of unconjugated estriol as indicative of impending preterm labor essentially as instantly disclosed.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have added or substituted estriol as the biochemical marker of impending delivery in the method of Leavitt et al., as modified above, because Leavitt et al. teach the general applicability of the method for any biochemical marker of impending delivery which can be assayed in a cervicovaginal secretion sample and Dullien teaches unconjugated estriol as such a marker. One would have been motivated to assay an alternative marker to fibronectins, as specifically taught in Leavitt et al., in view of the general applicability of the method taught in Leavitt et al. and the known ability of unconjugated estriol to serve as such a marker, particularly in view of the ease of repeated sampling of an alternative sample such as saliva to accomplish the determination of impending delivery taught in Dullien. One would have had an extremely reasonable expectation of success in using the method of Leavitt et al., as modified, in view of the teachings of the references. It would have been further obvious to have confirmed the indication of impending delivery from a saliva determination with a determination of both fibronectin and IGFBP-1 in a sample of cervicovaginal secretions because determination of ruptured fetal membranes is of unquestioned importance relating to the health of both the mother and the fetus and for the clinical management of pregnant patients, particularly in those patients

indicated as at risk for preterm birth wherein a decision regarding the use of tocolytic/ pregnancy-prolonging agents must be weighed (Leavitt et al., Weiner et al., or Andersen et al.).

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 7, 14, 17-19, 22-26, 45, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leavitt et al., in view of any of Johnson et al., Meis et al., or Keirse, and further in view of Weiner et al. or Andersen et al., as applied to claims 1-13, 15-19, 22-26, 30-31, 33-44, and 47-64 above, and further in view of Allen et al. (Exp. Biol. Med. 226: 498, 2001) or Olsen et al. (Lancet 339: 1003, 1992).

Claims 7, 14, 17-25, 30-34, 45, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leavitt et al., in view of any of Johnson et al., Meis et al., or Keirse, further in view of Weiner et al. or Andersen et al., further in view of Dullien, as applied to claims 1-13, 15-44, and 47-64 above, and further in view of Allen et al. (Exp. Biol. Med. 226: 498, 2001) or Olsen et al. (Lancet 339: 1003, 1992).

The teachings of Leavitt et al., Johnson et al., Meis et al., Keirse, Weiner et al., Andersen et al., and Dullien are as set forth above and differ from the invention as instantly claimed in not teaching omega-3 fatty acids as a pregnancy-prolonging agent.

Either of Allen et al. or Olsen et al. teach the efficacy of omega-3 fatty acid supplementation treatments in reducing preterm delivery.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have supplemented the diet of those patients with intact fetal membranes

indicated as at risk of having impending delivery with a pregnancy-prolonging agent because of the direct suggestion in Leavitt et al., as modified, to do so. One would have been motivated to treat a patient so identified with a known efficacious pregnancy-prolonging agent, such as omega-3 fatty acids as taught by either of Allen et al. or Olsen et al., in view of the direct suggestion to do so in Leavitt et al., as modified, and because one would have had an extremely reasonable expectation that a known efficacious pregnancy-prolonging agent would successfully perform its desired function of prolonging pregnancy in the method. It would have been further obvious to have administered a plurality of pregnancy-prolonging agents to the identified patients for the combined benefits of each agent.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any of Yemini et al. (Am. J. Obstet. Gynecol. 151: 574, 1985) or Noblot et al. (Eur. J. Obstet. Gynecol. Rep. Biol. 40: 203, 1991) also teach the efficacy of progesterone treatments in reducing preterm delivery.

Dullien (US 5,370,135) teaches determinations of unconjugated estriol as indicative of impending preterm labor essentially as instantly disclosed and teaches the determinations for monitoring the start and/or continuation of tocolytic therapy. However, progesterones are not specifically mentioned as a tocolytic/ pregnancy-prolonging agent.

Terao et al. (US 5,650,394) teach determinations of fetal fibronectin as indicative of impending preterm labor essentially as instantly disclosed and teach the determinations for monitoring the start and/or continuation of tocolytic, urinastatin, and antibiotic therapy. However, progesterones are not specifically mentioned as a tocolytic/ pregnancy-prolonging agent.

Lockwood et al. determined the level of fetal fibronectin in vaginal and/or cervical samples obtained from the cervical os and posterior fornix of control pregnant patients, patients with preterm rupture of fetal membranes, and patients with intact membranes having preterm contractions. Samples from the control population were obtained a plurality of times, average of four, between 5 and 40 weeks of gestation (page 670, bottom of column 1 and Figure 1). Between weeks 21 and 37 of gestation (i.e. preterm), elevated levels of cervicovaginal fetal fibronectin were correlated with either: preterm rupture of fetal membranes and impending delivery in patients; or, impending preterm delivery in patients with intact membranes (page 669, Abstract, and page 671, column 2). Lockwood et al. also determined fetal lung maturity in amniotic fluid samples obtained from control patients also monitored for cervicovaginal fetal fibronectin (page 670, bottom of column 1). The reference teaches that the detection of fetal fibronectin in patients with impending preterm delivery having intact membranes may be the result of release of fetal fibronectin from the chorion or from the extracellular matrix of the chorion-decidual membrane junction (Abstract, or pages 673-674). However, the reference does not teach the combined detection of fetal fibronectin and insulin-like growth factor binding protein 1 (IGFBP-1) in samples from the same patient, or kits with both anti-fetal fibronectin and anti-insulin-like growth factor binding protein 1 antibodies.

Senyei et al. (U.S. Patent No. 5,468,619; hereafter '619) teach the detection of total fibronectin in samples obtained from the cervical os and/or posterior fornix as indicative of impending delivery. However, the reference does not teach the combined detection of total fibronectin and insulin-like growth factor binding protein 1 (IGFBP-1) in samples from the same patient, or kits with both anti-fibronectin and anti-insulin-like growth factor binding protein 1 antibodies.

Kanayama et al. determined elastase as a marker of imminent delivery and the level thereof as a further indicator of impending premature rupture of membranes. However, the reference does not teach the combined detection of elastase and insulin-like growth factor binding protein 1 (IGFBP-1) in samples from the same patient, or kits with both anti-elastase and anti-insulin-like growth factor binding protein 1 antibodies.

Rutanen et al. (American Journal of Obstetrics and Gynecology 164(1): 258, Abstract no. 38, 1991) obtained cervical secretion samples from patients and determined, with sandwich immunoassays using two monoclonal anti-insulin-like growth factor binding protein 1 antibodies, the level of insulin-like growth factor binding protein 1 (IGFBP-1) in the samples for the purpose of diagnosing premature fetal membrane rupture. Rutanen et al. detected levels of IGFBP-1 in samples of cervical secretions in three ranges: undetectable in nonpregnant patients; a range of from undetectable to 90 ng/ml (i.e. 90 μg/l) in pregnant patients with intact fetal membranes with or without labor; and an increased level ranging from 175 to 20,000 ng/ml (i.e. μg/l) in pregnant patients with or without labor susceptible to delivery due to rupture of membranes. The reference also teaches levels of IGFBP-1 detectable in amniotic fluid, maternal serum, maternal urine, and seminal plasma.

Rutanen (WO 92/12426; hereafter '426) discloses a method and kit for the determination of fetal membrane rupture by determination of amniotic fluid presence in the vagina (e.g.: claims; ¶ bridging pages 3-4). In the method, a vaginal secretion sample is obtained from a patient and the level of insulin-like growth factor binding protein 1 (IGFBP-1) in the sample is determined by immunoassay, preferably using two monoclonal anti-insulin-like growth factor binding protein 1 antibodies. The test can be so designed that sources of IGFBP-1 other than amniotic fluid, such as blood, cannot cause false positive results in the test conditions used (pages 10-15; ¶ bridging pages 3-4). Rutanen ('426) also teaches the importance of diagnosis of premature fetal membrane rupture (page 1) with regard to increased risk of infection and increased mortality.

Rutanen et al. (Clinica Chimica Acta 214(1): 73, 1993), with sandwich immunoassays using two monoclonal anti-IGFBP-1 antibodies, selected from 6303 and 6305 (e.g. page 75), one of which was labelled, provided in a kit, detected levels of IGFBP-1 in samples of cervical secretions, extracted into 0.5 ml of diluent, in various ranges (e.g. pages 76-78): undetectable (i.e. < 0.5 μg/l) to < 1 μg/l in nonpregnant patients; a range of from undetectable (i.e. < 0.5 μg/l) to detectable (i.e. ≥ 0.5 μg/l) up to 90 μg/l (median 8.6 μg/l) in pregnant patients with apparently intact fetal membranes and not in labor (i.e. of normal or low susceptibility to delivery soon); and, an increased level greater than 100 μg/l ranging from 175 to 20,000 μg/l in pregnant patients highly susceptible to delivery due to rupture of fetal membranes. The reference teaches the decidual cell production of IGFBP-1 (e.g. Fig. 3, and page 80) and the chorionic membrane production of fetal fibronectin. The reference suggests that, as does fetal fibronectin, IGFBP-1 may leak into the vagina when the cervix dilates and the chorion is detaching from the decidua in the lower uterine segment (page 80).

Rutanen et al (Clinica Chimica Acta 253: 91, 1996) teach a dipstick sandwich immunoassay using monoclonal anti-IGFBP-1 antibodies 6303 and 6305 for detection of ruptured fetal membranes.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James L. Grun, Ph.D.
February 6, 2006

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